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**Manuscript title: Comprehensive Lifestyle Intervention vs. Soy
Protein-based Meal Regimen in Patients with Non-alcoholic
Steatohepatitis**

Manuscript number: 43200

Dear editors,

we are very pleased with the results of the evaluation by the reviewers.

Please find the changes kindly suggested by the reviewers marked in red in the manuscript. Also the format changes have been done according to the WJG guidelines.

In the following we respond to the reviewers' comments. All points have been addressed, our answers are marked in blue and italics, citations of the manuscript are held in red.

Reviewer #1: Here Deibert P. et al present a clinical study in which 22 patients with NAFLD are randomly assigned either to meal-replacement (MR) with a soy-yogurt-honey preparation or to guided lifestyle change with endurance activity and nutrition counselling. Anthropometric and biochemical indices, as well as internal and liver fat content as determined by MR, are successfully affected by both therapeutic strategies although with some differences.

I have the following points:

1) How was NASH diagnosed? On page 8, it is stated that "patients eligible for the study were obese adults with BMI between 30 and 40 and with sonographic findings of fatty liver as well as elevated liver enzymes". This is clearly not sufficient for a diagnosis of NASH. Conversely, on page 13, it is stated that patients were extracted among those already diagnosed as NASH, although it is

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not specified how the diagnosis of NASH has been done. This point should be clarified, and the discrepancy between the two statements should be solved

In the methods paragraph a further sentence has been added: Daily alcohol consumption had to be less than 20g in males and less than 10g in females. Secondary causes of fatty liver disease other than overweight and obesity were excluded by anamnesis. This is the reason for further elimination of eligible probands made through telephone interviews. This is added in our CONSORT flow chart Figure 1.

2) The specific composition of the soy-yogurt-honey preparation should be presented (grams of components, calories, etc...)

To keep the text on size (4th point of reviewer's demand) literature 26 was supplemented. A detailed description of the preparation was made available, as well as an extensive instruction for the meal replacement strategy.

3) Results are redundantly presented in the text and in the tables. If numerical data are provided in the tables or figures, the text should be used only for the narrative presentations of results, referring to tables or Figure for numbers

Redundant numerical data were deleted and the result section was shortened.

4) All the sections of the text are excessively long and should be significantly shortened

All sections except the method section were shortened where appropriate (details were added, as described above). The authors agreed that a detailed description of the spectroscopy is necessary as it was the first time this method was used in humans.

Reviewer #2: The article analyzes the influence of the comprehensive lifestyle intervention vs. soy protein-based meal regimen in patients with non-alcoholic steatohepatitis. 36 patients with NASH participated in a randomized single-center study. They were randomly assigned either to the meal replacement group with soy-yogurt-honey preparation or to the guided lifestyle change group with endurance activity and nutrition counselling. To solve this problem the authors have chosen an adequate research approach. The authors measured serum alanine transaminase (ALT), aspartate transaminase (AST), lipid parameters and adipokines; liver fat content and lipid composition by magnetic resonance imaging and magnetic resonance spectroscopy. Statistical analyses were conducted with SPSS software. Results were expressed as median interquartile range. The obtained results are discussed in-depth taking into account the latest data found in scientific publications on the investigated problem. The authors proved that comprehensive lifestyle intervention and meal

replacement regimen have comparable effects on body and liver fat, as well as decrease in markers of hepatic inflammation among NASH patients. The more important results of investigation reflected that internal fat and hepatic lipid content were markedly reduced in both groups in comparable amount. There was a strong correlation between reduction in liver fat and decrease in ALT. Changes in adipokines, particularly in adiponectin and leptin were closely related to intrahepatic lipid changes. . The authors devised the lifestyle program for patients of the change group. According to this program they attended 6 weekly teaching sessions about nutrition and physical exercise. The article is devoted to the subject of NASH prophylaxis, has practical significance and is illustrated with 4 figures and 2 charts. The material is presented logically and correctly. I recommend the article for publication.

Reviewer #3: Non-alcoholic steatohepatitis (NASH) has nowadays become an epidemic. Apart from the presence of fat in the liver it is characterized by augmented intrahepatic inflammation and exacerbated hepatocellular injury. The presence of NASH in the liver is associated with an increased possibility of development fibrosis, cirrhosis or even neoplasia. Taking that there is no clearly defined strategy among physicians for the prevention or treatment of NASH, studies focusing to this direction are of major importance. So far, physical activity or weight loss are recommended as potential interventions able to improve liver histology in NASH patients. In the present manuscript by Deibert et al, the authors have made an very good attempt to explore and compare the role of Lifestyle Intervention vs. Soy Protein-based Meal Regimen in the improvement of liver pathophysiology of Patients with Non-alcoholic Steatohepatitis. The paper is well written and thought out, clearly organized and structured, acknowledges appropriately other studies regarding the same subject and ends up in reasonable conclusions. In addition, the study is of high interest due to its direct clinical implications and the authors used correct methodology. Therefore my opinion and evaluation is positive. However, I still have some comments:

-The caloric input of the participants, especially during the first 6 weeks of the interventions differed significantly between the 2 groups. How could the authors explain that the observed effect in liver pathophysiology and parameters was indeed related to meal replacement and not to the extensive caloric restriction that the patients underwent?

It was not possible to distinguish between an effect of weight loss due to marked caloric restriction or soy-based meal replacement. This point was added in the study limitations in the discussion:

Moreover, it was not possible to ascertain whether the caloric restriction in the MR-Group or a specific effect of the soy-yogurt-honey preparation led to the different composition of liver fat. However, our study once more confirmed, that with a supplementation of high quality proteins a significant weight reduction without loss of muscle mass is achievable.

Our study compared two different weight-reduction strategies: therapeutic lifestyle-change (i.e. caloric restriction combined with increased physical activity) with a meal replacement strategy (caloric restriction in form of a soy protein based meal replacement). We also added this clarification in the last paragraph of the introduction.

-To the same direction, did the authors perform any kind of clinical, radiological or biochemical measurements in any intermediate timepoint within the 24 weeks (especially after the first 6 weeks that the interventions pertinent to calories differed significantly)?

*As the primary end point was the status **after** sufficient weight reduction in order to assess the possible long term effects, no interim analysis was done. The aim of the study: "The effects of a **significant weight loss after 24 weeks** on liver fat content....." was now clearly stated in the last paragraph of the introduction).*

-How did the authors choose the type of exercise that was applied to the participants?

*Endurance training was considered to be most appropriate and suitable for NASH patients. Most of these patients are not engaged in sports, thus the motivation for vigorous exercise would be difficult to sustain. We added the following clarification to the description in the method section: **The group-based exercise sessions were led by a sport physiologist. Each participant was instructed to walk at a specific heart rate reflecting 60-75% of the individual VO_{2max}.***

We submit the revision of our paper to the World Journal of Gastroenterology and are thankful for the opportunity to publish our work in this valuable journal.

Yours sincerely


Peter Delbert